SUMMARY MINUTES

OF THE

OBSTETRICS AND GYNECOLOGY DEVICES

ADVISORY PANEL MEETING

SIXTY-THIRD MEETING

OPEN SESSION

January 29, 2001

Gaithersburg Marriott Hotel
Gaithersburg, Maryland

Obstetrics and Gynecology Devices Panel
January 29, 2001

Panel Chairperson
Jorge D. Blanco, M.D.
Magella Corporation/PeriNatal Associates of Texas

*Ralph B. D'Agostino, Ph.D.
Boston University

*Michael P. Diamond, M.D.
Hutzel Hospital/Wayne State University School of Medicine

Grace M. Janik, M.D.
Medical College of Wisconsin

David F. Katz, Ph.D.
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*Barbara Levy, M.D.
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*Michael Neuman, M.D., Ph.D.
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College of Nursing, Villanova University

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Ob/Gyn Associates

Consumer Representative
Diony S. Young
Editor, Birth: Issues in Perinatal Care

Industry Representative
Cindy Domecus, R.A.C.
Conceptus, Inc.

*Temporary Voting Members

FDA Representatives

Elisa Harvey, D.V.M., Ph.D.
Panel Executive Secretary

Joyce Whang, Ph.D.
Obstetrics and Gynecology Devices Branch

Daniel Schultz, M.D.
Acting Director, Division of Reproductive, Abdominal, and Radiological Devices

Colin Pollard
Chief, Obstetrics and Gynecology Devices Branch

Cmdr. Diane Mitchell, M.D.
Medical Officer, Obstetrics and Gynecology Devices Branch

Veronica Price
Biomedical Engineer, Obstetrics and Gynecology Devices Branch

Richard Kotz
Division of Biostatistics

OPEN SESSION—JANUARY 29, 2001

Panel Chair Jorge D. Blanco called the Open Session to order at 9:17 a.m., asking panel members to introduce themselves and state their areas of expertise. **Outgoing Panel Executive Secretary Dr. Elisa Harvey** introduced **new Executive Secretary Dr. Joyce Whang**, and listed tentative future panel meeting dates as May 21 and 22, July 16 and 17, and October 15 and 16, 2001. Dr. Harvey read appointments to temporary voting status for Ralph B. D'Agostino, Ph.D., Michael P. Diamond, M.D., Barbara Levy, M.D., Michael Neuman, M.D., Ph.D., and Gerald Shirk, M.D. Dr. Harvey also read the conflict of interest statement, noting that the FDA had granted waivers to Drs. Diamond and Levy and to Nancy C. Sharts-Hopko, Ph.D., for their interests in firms potentially affected by the day's deliberations and that unrelated matters involving Drs. Levy and Sharts-Hopko had been considered and their full participation allowed.

Colin Pollard, chief of the Obstetrics and Gynecology Devices Branch, acknowledged and thanked outgoing Panel Executive Secretary Elisa Harvey and Acting Division Director Daniel Schultz from the FDA and presented plaques of appreciation to outgoing panel members Donald Chatman, M.D., (who was not present), Consumer Representative Diony S. Young, Grace M. Janik, M.D., and Industry Representative Cindy Domecus, R.A.C. He updated the panel on developments since the panel meeting in January 2000, noting that the Mallinckrodt premarket approval application (PMA) for a fetal oxygen saturation monitor was approved in May and that the FDA had participated in a June conference on effectiveness of condoms in prevention of sexually transmitted diseases and was engaged in a condom labeling review.

Mr. Pollard read the charge to the panel: to consider a PMA by CryoGen for the FirstOption™ Uterine Cryoblation Therapy System for abnormal (benign) uterine bleeding (AUB). He gave background information on AUB, explaining the usual patient workup and medical or surgical management procedures. Hysteroscopic endometrial ablation using lasers has been a surgical option since the 1980s, but new devices with new intended uses have presented new safety and efficacy questions, which has necessitated a switch from the 510(k) regulatory pathway to the PMA approach. New design features of such devices have produced simpler, shorter procedures but provide less surgical feedback. Since a 1995 panel meeting that recommended revised guidance, initial safety studies, and pilot studies, there have been many devices under development; of these, the FirstOption™ is the first cryosurgical device to apply for premarket approval. The FDA asked for panel guidance on the aspects of use and forms of evidence necessary for approval.

OPEN PUBLIC HEARING

There were no requests to address the panel.

PMA P000032--CRYOGEN FIRSTOPTION™ UTERINE CRYOBLATION THERAPY SYSTEM

Sponsor Presentation

David Murray, president and CEO of CryoGen, Inc., discussed endometrial ablation for uterine bleeding and reviewed statistics on the history of cryosurgery. He showed a video of the FirstOption™ procedure, stating that cryosurgery requires less anesthesia than the Rollerball alternative and that the quality of life is significantly improved.

Gene Reu, CryoGen vice president for research and development, gave an overview of the technology, explaining design principles of the console, cryoprobe, and disposable control unit. A clinical device assessment performed during the clinical study revealed device reliability issues, most of which have been validated as resolved, with two still outstanding. He concluded that these issues had a minimal impact on treatment and that design validation showed the reliability issues can be and have been addressed.

Cheryl Shea, CryoGen vice president for regulatory affairs and quality assurance, reviewed the history and current status of the regulatory and quality system issues, noting that this is a preamendment Class II device seeking a PMA approval for endometrial ablation. She gave an overview of the preclinical *ex vivo* and early *in vivo* data provided by bench testing in gelatin and beef liver and extirpated human uteri and *in viv*o in goat liver. She explained the multicenter study procedure and the proposed indication for use.

Dr. Martha Heppard, director of the Inverness Women's Health Center in Denver, Colorado and clinical trial investigator, explained the multicenter clinical study. Effectiveness endpoints were a quantitative pictorial assessment of bleeding, clinical success, and impact on quality of life. Safety endpoints were incidence and severity of adverse events reported during the study. The equivalence study was designed to show a two to one randomization of device to Rollerball for 275 patients at 10 sites. Patients were treated preoperatively with Lupron and assessed at two weeks, and three, six and 12 months with pictorial blood assessment charts and quality of life instruments. Dr. Heppard explained inclusion and exclusion criteria, which were consistent with other studies and FDA guidance documents. Clinical success was based on 12-month follow-up data and a conservative

definition of success. Dr. Heppard explained the statistical evaluation parameters and formal test of hypothesis. Dr. Heppard also discussed patient enrollment accountability and demographics, noting that the only significant variable was a much higher median preoperative bleeding rate in the Cryoblation group.

Dr. Heppard summarized study results, which showed that Cryoblation is statistically equivalent to Rollerball with respect to 12-month success. Accountability at 12 months was good, and acute treatment success rates were high, although a lower success rate was noticeable at two study sites for both investigational and control groups. There was significant improvement in mood, pre-menstrual syndrome, cramping, and quality of life postoperatively for both groups. No unanticipated averse events were reported for either group. Anticipated serious adverse events were comparable for both groups. Safety benefits included a statistically significant difference in the amount of anesthesia needed for the investigational device group.

David Murray concluded the sponsor presentation by noting that the clinical study data met the hypothesis and demonstrated effectiveness and safety with no serious adverse events and significant patient satisfaction with quality of life.

Questions from the panel to sponsors included the proportion of the uterine cavity treated by probe during the procedure and the importance of uterine cavity size, the timeframe of the freeze process, the extent of the freezeball, and the rate of heating time. There were also questions relating to the enrollment and randomization process.

FDA Presentation

Veronica Price, biomedical engineer and lead PMA reviewer, introduced the FDA review team and explained that the PMA was submitted in modules with the company

working interactively with the Agency. Modules on general information, device description, manufacturing information, and product development testing have been reviewed and closed. After briefly reviewing system components and key performance specifications, Ms. Price noted that the procedure is used with adjunctive ultrasound according to specified clinical protocol parameters. She analyzed device experience during the multicenter study, which included a number of device failures and malfunctions. Analysis of investigator complaints and clinical device assessment reports showed various types of user errors and root causes, which she enumerated. The sponsor has taken corrective actions such as software modifications, design and specification changes, additional operator training, and different labeling. Ongoing device refinements include the gas mix compressor circuit obstruction, disposable control unit attachment, and user errors. Ms. Price concluded with two questions for the panel on the impact of device malfunctions on the trial and on the confidence level in reliability of the commercial design.

Richard Kotz of the Division of Biostatistics gave the statistical review of the pivotal trial. He outlined study design and hypothesis, noting that sample size was based on an equivalence study with an acceptable clinical difference of 20%. Analysis of study results overall and stratified by age and site showed that the sponsor met the objective of the primary endpoint and detected no significant differences between patients under and over 40, although the study was not powered to detect those differences. Success rates differed significantly across sites, with two sites (Boston and Alabama) having very poor results, possibly because of in-office use or use without an ultrasound technician. He noted that there were also observed enrollment anomalies at two sites (Denver and Alabama).

Diane Mitchell, M.D., obstetrician/gynecologist in the Office of Device Evaluation, gave the clinical review. She looked at safety in terms of perioperative serious and nonserious adverse events, thermal safety and effectiveness, and ultrasound use. She noted some discrepancy in higher pain and cramping results for the Cryoblation device than for the control, but other adverse event rates were not significant. Dr. Mitchell also stated that thermal safety results in the pre-hysterectomy study provided no evaluation of additional freezes, but pivotal study data showed use of longer or additional freezes, and device malfunctions occurred with the majority of these protocol deviations. She noted device design features that allow for more than two freezes and automatic shut-off occurring only after 10 minutes. Observing that ultrasound should be used with the device to monitor the ice front and detect perforation, Dr. Mitchell stated that labeling would include use of the ultrasound but that it should be noted that a second pair of hands is needed and the device operator must be experienced in looking at ultrasounds.

Dr. Mitchell looked at effectiveness in terms of success rates and understanding the study results. She said that success rates, while meeting study endpoints, must be understood in terms of study limitations, which include device malfunctions and outlier sites. She listed labeling concerns, which include contraindications, possibly on uterine size, possible prophylactic antibiotic use, issues such as recommendations on anesthesia use and need for dilation, and suggestions on physician training. Dr. Mitchell listed ongoing FDA review issues such as adverse events, labeling and training information, malfunctions analysis, Bioresearch Monitoring inspections, and incomplete patient follow-up.

Questions from the panel to both sponsors and FDA included whether there was a preponderance of adverse events at the two sites with lower success rates, to which sponsors replied there was not, and whether the lower success rate in the control arm affected results for the investigational arm, to which sponsors replied it did not. The panel also noted that clinical safety should be tested under conditions of actual use, such as use of Lupron pretreatment, and that labeling should be revised on the failsafe mechanism for shut-off after 10 minutes of use. Another panel question involved whether the product can make the claim it requires less anesthesia, given results, and whether patients receiving cryotherapy truly experienced less pain. Questions on randomization procedures and tables were addressed, and issues involving the need for two people to ensure proper ultrasound use and proper credentialing of operators were also raised.

FDA Questions for Panel Discussion

1) *Has the sponsor adequately addressed the issue of device reliability? If not, what additional studies does the panel recommend? Should labeling incorporate information regarding failure rates or need for multiple units?*

The panel recommended that sponsors provide reliability data to the FDA to show that problems have been fixed and clinical data to show that the modified device used in the field has an acceptable malfunction rate.

2) *Is the standardization of the procedure critical to device safety and treatment success? Should the device be designed to assist the investigator in performing only the number and duration of freezes specified in the clinical trial protocol?*

While acknowledging that physician variability will occur, the panel recommended that standardization of the procedure technique should be clearly expressed in the labeling. It was also suggested that the timing beep should provide more information, such as how long the procedure has continued. The panel stated that data from the two sites with bad results should be analyzed in terms of pretreatment and operator skill or experience to see why their rates were markedly different and if appropriate that the data should be included in the labeling. The labeling should also be modified to clarify the failsafe shut-off feature and to clarify the need for pretreatment thinning of the endometrium and for providing traction or pressure.

3) *Are there any recommendations for training or labeling to achieve more uniform success rates?*

The panel recommended that labeling clearly indicate that the purpose of the device is to reduce, not eliminate, menstrual flow. The panel did not have enough information to make recommendations for training and labeling, but urged that the company and the FDA should address the reasons for the variation in success rates.

4) *Do the 12-month success rates show that the device provides clinically significant results?*

The panel agreed that the sponsors met the criteria given them for success rate, while suggesting that it would behoove the sponsors to look at sites achieving lower success rates.

5) *Was the incidence of adverse events in the treatment arm acceptable?*

The panel had no problem with the incidence of adverse events in this trial but suggested that the issue of patient expectations on level of pain or discomfort should be addressed in labeling and documentation.

6) Is the proposed labeling adequate? Do you have recommendations for changes?

The need for revised labeling was a major issue for the panel. The panel recommended that labeling be revised to provide an objective, balanced, and accurate reflection of the clinical data that would show alternative treatments fairly. Concern over the name FirstOption™ was expressed. Another recommendation was to make the language of the patient brochure consistent with that of the user's manual. Standardization of preoperative and operative procedures was recommended, as was revision of contraceptive warnings to make patients aware of risks if they do achieve pregnancy. Ultrasound should be listed as mandatory, and device use should be limited to physicians experienced with D & C, uterine surgery, and ultrasound. References to use of less anesthesia and prophylactic antibiotics should be struck, because there are no data to back up claims. Indications for use should note the device is for abnormal bleeding in a patient with a normal endometrium, should indicate some screening for abnormalities and structural pathologies, and should specify a 10 cm or smaller uterus, if this is consistent with study data. Contraindications on prior C-sections should be reworded.

7) Please identify important aspects of physician training.

The panel stressed that physicians should be experienced in use of D & C procedures, uterine surgery, and ultrasound. Physicians should be experienced in dealing with intramural myomas, position or placement of myomas that make ultrasound visualization difficult, and pathology outside the cavity that could compromise the procedure, and they should be trained in what to do if perforation occurs.

8) Is the proposed follow-up plan adequate to address issues of long-term safety and effectiveness?

The majority of the panel wanted to follow the current set of patients for three years, although there was one member who wanted long-term follow-up of all patients. In addition, the panel recommended that the company provide data showing a lower malfunction rate in the field. Some members also wished for intermediate data on site variations.

OPEN PUBLIC HEARING

There were no requests to address the panel.

Final Sponsor Remarks

David Murray stated that the sponsors do intend to revise labeling to specify length of procedure and would look carefully at modification of labeling to allow physician flexibility but would specify technique in other areas. He stressed that validation of changes had been performed on most issues and noted that the device in commercial use was not substantially different from that in the clinical study. He thanked the panel for its review.

Final FDA Remarks

Dr. Schultz thanked the panel for a complete and helpful discussion and for its clear direction on the need for validation of changes producing the desired results and for labeling changes. He stated that the FDA would work with sponsors to implement the panel's recommendations.

Panel Vote and Recommendations

Dr. Harvey reviewed the definitions of safety and efficacy and valid scientific evidence and outlined voting options.

A motion was made and seconded to recommend the PMA as approvable with conditions. The following conditions were made, seconded, and passed:

1) That a premarket prospective study be performed to evaluate all 18 device malfunctions and show that the device malfunction rate has been corrected.

2) That premarket standardization and documentation of technique be required and that modification of the technique be explained in the manual.

3) That postmarket analysis of the standardized technique with the revised device be done to address intersite variability, with a minimum of a six-month follow-up.

4) That the indication for the device read for the reduction of bleeding.

5) That labeling in both patient and physician brochures be extensively revised according to panel discussion.

The motion to recommend the PMA as approvable subject to the above conditions passed.

Consumer Representative Diony Young asked about informed consent documentation on the device. Dr. Schultz replied that the patient information brochure would contain the necessary information for informed consent.

Panel Chair Dr. Blanco thanked the panel and presenters and adjourned the Open Session at 4:00 p.m.

I certify that I attended the Open Session of the Obstetrics and Gynecology Devices Advisory Panel Meeting on January 29, 2001, and that this summary accurately reflects what transpired.

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Elisa Harvey, D.V.M., Ph.D.
Panel Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

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Jorge D. Blanco, M.D.
Panel Chair

Summary minutes prepared by
Aileen M. Moodie